AMENDMENTS TO THE DRAWINGS

Kindly replace the drawing sheets containing Figures 8D, 9A, and 12C with the replacement sheets filed herewith. As required by 37 C.F.R. § 1.121(d), each sheet is labeled "Replacement Sheet" in the top margin.

REMARKS

Claims 15, 16, 20, 21, 29, 30, 42, 45-49, 51, 54, and 55 are pending. Due to a Restriction Requirement, all pending claims except claim 29 have been withdrawn from consideration. In an Office action mailed July 28, 2006, claim 29 was examined. Claim 29 stands rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter. Claim 29 is also rejected under 35 U.S.C. § 103 as unpatentable over Seino et al., *Ann. Surg.* 234:681-688, 2001 (hereafter "Seino") in view of Heinke et al., *Cardiovasc. Res.* 49:127-134, 2001 (hereafter "Heinke") and, further, as unpatentable over Chao et al., *J. Biol. Chem.* 277:31639-31645, 2002 (hereafter "Chao"). The Office also objects to the specification for failing to contain an abstract. The drawings are objected to as not being of sufficient quality. Each of these rejections and objections is addressed below.

Objection to the specification

The specification is objected to for failing to contain an abstract as required by 37 C.F.R. § 1.72(b). Applicants' records indicate an abstract was filed with International Application No. PCT/US2003/036624, of which the present application is the U.S. national stage. Applicants note that the abstract filed in the International Application appears on the cover page of the corresponding publication, WO 2004/045530. Further, a copy of the cover page of WO 2004/045530 appears in the image file wrapper of the present application on the Patent Application Information Retrieval (PAIR) system, and is

identified as "Abstract" and is dated May 9, 2005. Thus, Applicants submit that the present application contains an abstract, and this objection may be withdrawn.

Objection to the drawings

The Office objects to Figures 8D, 9A, and 12C, asserting that these figures are not of sufficient quality. Applicants accordingly provide revised figures and an amendment directing their entry into the application. This amendment adds no new matter. The objection to the drawings may also be withdrawn.

Rejection under 35 U.S.C. § 101

The Office rejects claim 29 as being directed to nonstatutory subject matter. In particular, the Office asserts that claim 29 encompasses a human being having a naturally occurring mutation that results in the expression of a dominant negative FADD protein. Applicants have amended claim 29 to recited a cardiomyocyte expressing a recombinant dominant negative FADD protein, thus rendering this rejection moot. Support for this change may be found, for example, at page 30, line 26-27, of the specification. The rejection under 35 U.S.C. § 101 may be withdrawn.

Rejection under 35 U.S.C. § 103(a) over Seino in view of Heinke

The Office rejects claim 29 as being obvious over Seino in view of Heinke. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there

must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143. The cited references fail to teach all claim limitations and fail to provide a reasonable expectation of success, as outlined below. The obviousness rejection over Seino in view of Heinke should therefore be withdrawn.

Seino and Heinke

Seino teaches dominant negative FADD (dn-FADD) expression in liver cells of a mouse following adenoviral vector transduction. Seino discloses that dn-FADD expression in liver cells inhibits apoptosis without affecting NF-κB expression. Seino does not teach expression of dn-FADD in tissues other than liver, nor does Seino teach a cardiomyocyte, expressing dn-FADD. Thus, Seino fails to teach the present invention, i.e., an cardiomyocyte expressing recombinant dn-FADD.

Heinke teaches that FADD expression and apoptosis are increased in a canine pacing model of heart failure. While the Office asserts (page 5 of the action) that Heinke teaches that overexpression of Fas, FAS-L, and FADD results in increased apoptosis observed in the canine model, Applicants find no such disclosure in this reference. Rather, Heinke observes a correlation between apoptosis and increased FADD expression

but provides no evidence of causal relationship between the two. Further, Heinke does not teach expression of dn-FADD, does not teach cells (e.g., a cardiomyocyte) expressing dn-FADD, and does not indicate that apoptosis in the heart can be reduced by decreasing FADD expression or activity or by expression of dn-FADD. Thus, Heinke also fails to teach the present invention.

The combination of references fails to teach all claim limitations

To render an invention obvious, the reference or combination of references must teach all claim limitations. No combination of Seino and Heinke teaches or suggests a cardiomyocyte expressing recombinant dn-FADD. As Seino and Heinke fail to teach all limitations of the present invention, these references cannot render claim 29 obvious. On this basis, the obviousness rejection should be withdrawn.

There was no reasonable expectation that dn-FADD can reduce apoptosis in cardiomyocytes

An invention is unobvious if there is no reasonable expectation of success, based on a lack of predictability at the time of filing. M.P.E.P. § 2143.02. The present specification indicates that activity of FADD is cell-type specific (see page 32, line 22 through page 34, line 8). In cardiomyocytes, Applicants have discovered that FADD inhibits TNF-α-induced activation of NF-κB without affecting baseline NF-κB activity. This is not true in all cell types. In smooth muscle cells, for example, FADD does not inhibit TNF-α-mediated NF-κB activation (page 33, lines 24-25). In HEK293 cells, viral

expression of FADD alone in the absence of TNF-α was sufficient to induce nuclear translocation of NF-κB (page 34, lines 1-4). Thus, FADD activity cannot be predicted in one cell type based on its activity in another.

The cell-type specific nature of FADD activity, and corresponding unpredictability, is reflected in Seino. Whereas TNF-α-induced NF-κB activation in cardiomyocytes is reduced by dn-FADD (page 36, lines 13-16 of the specification), Seino observes that TNF-α-induced NF-κB induction in the liver is not reduced by dn-FADD. Thus, it is simply impossible to conclude what effect FADD (or dn-FADD) expression would have in a particular cell type *a priori*. Seino thus does provide a reasonable expectation of success and cannot be used to render the present invention obvious.

Heinke does not rectify the unpredictability of FADD/dn-FADD activity in different cell types. Both the model used by Heinke and the results described in Heinke are problematic in this regard. Heinke employs a pacing model, which may not be applicable to most cardiac diseases. In the pacing model, normal cardiac function can be restored simply by cessation of pacing. By contrast, pacing can be beneficial in ischemic injury. For this reason, one of skill in the art could not conclude the results generated by Heinke would apply to most cardiac disease.

Even setting aside the potential problems with the model employed by Heinke, this reference does not show that reduced FADD expression or activity would result in a corresponding reduction in apoptosis. As FADD activity is governed by its interactions with other proteins (e.g., Fas), rather than by its absolute level within the cell, expression

changes alone do not indicate a corresponding effect on FADD activity directly or on its downstream effectors. Further, Heinke is silent with regard to the effect of reduced FADD expression or the effect of dn-FADD expression in cardiomyocytes. One could not conclude from Heinke, either alone or in combination with Seino, that reducing FADD levels in cardiomyocytes or that expression of dn-FADD in cardiomyocytes would reduce apoptosis. For all of these reasons, the combination of Seino and Henke cannot render the present invention obvious.

Rejection under 35 U.S.C. § 103(a) over Chao

The Office also rejects claim 29 as obvious over Chao. Applicants traverse this rejection on the basis that Chao is not prior art under 35 U.S.C. § 102, as this reference represents Applicants' own work published less than one year before filing. In support of this traverse and pursuant to M.P.E.P. § 2132.01, Applicants provide an unsigned Declaration under 37 C.F.R. § 1.131 of Dr. Anthony Rosenzweig. In view of the Declaration, Applicants submit that this rejection should be withdrawn pending receipt of a signed copy of the Declaration.

CONCLUSION

Applicants submit that claim 29 is in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for three (3) months, to and including January 29, 2007, and a check in the amount of $510.00 in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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